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Year: 2017

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Knechtle, B

DOI: [https://doi.org/10.1007/978-3-319-28265-7\\_10](https://doi.org/10.1007/978-3-319-28265-7_10)

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ZORA URL: <https://doi.org/10.5167/uzh-126748>

Book Section

Accepted Version

Originally published at:

Knechtle, B (2017). Ultra-marathon running: Medical issues. In: Feletti, Francesco. Extreme Sports Medicine. Springerverlag: Springer, 151-162.

DOI: [https://doi.org/10.1007/978-3-319-28265-7\\_10](https://doi.org/10.1007/978-3-319-28265-7_10)

## **Ultra-marathon running: Medical issues**

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## **Abstract**

An ultra-endurance performance is defined as any performance lasting for longer than six hours. Ultra-marathons can be held as single stages races in distance- and time-limited races and as multi-stage races. The longest ultra-marathons cover several thousands of kilometres and can endure for up to two months. Ultra-marathoners were generally men, have a mean age of ~45 years, are married and are well educated where percentage of female finishers is at ~20%. Ultra-marathoners are different to marathoners regarding anthropometry and training where ultra-marathoners complete more running kilometers in training than marathoners do, but they run more slowly during training than marathoners. Apart from anthropometric characteristics such as body mass index and body as well as training characteristics such as volume and speed during running training, previous experience is the most important predictor variable for successful ultra-marathon performance. Generally, women compete slower than men in ultra-marathon running; however, women were able to reduce the sex gap in recent years. The fastest race times are achieved at 35-45 years for both women and men. Generally, ultra-marathoners are not able to meet their energetic demands during a race and a partially considerable energy deficit results. The main running-related musculoskeletal injuries in ultra-marathoners were Achilles tendinopathy and patellofemoral syndrome. Although we know a lot about physiology, anthropometry, training and performance in these ultra-marathoners, we do not know why these persons compete in these races, what motivates them and why the number of master ultra-marathoners increases across years.

### **What is an ultra-marathon?**

An ultra-marathon can be defined as any athletic event involving a running distance longer than the traditional marathon length of 42.195 kilometers [1]. An ultra-marathon can also be defined as any running competition lasting longer than six hours where six hours and longer is defined as an ultra-endurance performance.

Ultra-marathons can be held as distance-limited races in kilometers or miles and in time-limited races in hours or days [1]. The most often held ultra-marathons in distance-limited races are races in 50km, 100km, 50 miles and 100 miles. However, there are also longer races up to 1000 km and 3100 miles. For the time-limited races, these are held as 6-hour, 12-hour, 24-hour, 48-hour, 72-hour, 6-day, and 10-day races as the most common durations.

### **Who are ultra-marathoners?**

In recent years, Hoffman systematically investigated socio-demographic characteristics of ultra-marathoners [2,3]. In a survey completed by 489 of 674 runners competing in two of the largest 161-km ultra-marathons in North America, respondents had a mean age of 44.5 years and were generally men (80.2%), married (70.1%), had bachelor's (43.6%) or graduate (37.2%) degrees [2]. In the ULTRA-Study, Hoffman and Krishnan [3] interviewed a total of 1,345 current and former ultra-marathoners. Median age at the first ultra-marathon was 36 years, and the median number of years of regular running before the first ultra-marathon was seven [3]. The age at the first ultra-marathon did not change across the past several decades, but there was evidence of an inverse relationship between the number of years of regular running before the first ultra-marathon and the calendar year [3]. The active ultra-marathoners had a previous year median running distance of 3,347 km, which was minimally related to age but mostly related to their longest ultra-marathon competition of the year [3].

## **Women in ultra-marathons**

The share of women competing in ultra-marathons was very low in the beginning of ultra-marathon running. In 161-km ultra-marathons held in the USA, the participation among women increased from virtually none in the late 1970s to nearly 20% since 2004 [4]. Their percentage is now at ~20% [4-6]. In two of the toughest ultra-marathons in the world, women accounted on average for ~21.5% in 'Badwater' and ~10.8% in 'Spartathlon' [5]. In most ultra-marathons, the number of female finishers increased across years [5,6]. For example, in the 'Swiss Alpine Marathon' in Switzerland, women's participation increased from ~10% in 1998 to ~16% in 2011 [6]. In 'Badwater' and 'Spartathlon' there was an increase in female participation in 'Badwater' from 18.4% to 19.1% and in 'Spartathlon' from 11.9% to 12.5% [5]. The rather low female participation might have different reasons. A potential explanation might be motivation. Female ultra-marathoners were task-oriented, internally motivated, health, and financially conscious individuals [7]. Men, however, trend rather to compete in order to beat a concurrent or to win a race.

## **Where are ultra-marathons held?**

Ultra-marathon races are offered all-over the world. There are some of the most famous races such as the 'Badwater' (held in USA), the 'Spartathlon' (held in Greece), and the 'Marathon des Sables' (held in Morocco) just to name the best known [1]. Some of these races are held under extreme conditions such as extreme heat [8]. A problem of races held in heat is the fact that performance will be impaired [9,10]. A very recent study showed that athletes would benefit from heat acclimation. Exposure to at least 2 h of exercise-heat stress on at least two occasions in the days may help preventing exertional heat illnesses and optimising performance outcomes in ultra-endurance runners in multi-stage ultra-marathon competition in the heat [11].

## **Where do ultra-marathoners originate from?**

It is well known that East-African athletes such as Kenyans and Ethiopians dominate the marathon events all over the world for decades [12,13]. In ultra-marathon running, however, athletes from other regions were dominating both participation and performance. For example, in 100-km ultra-marathons, most of the finishers originated from Europe, in particular from France [14]. The number of finishers from Japan, Germany, Italy, Poland and the United States of America increased exponentially between 1998 and 2011. For women, runners from Canada became slower while those from Italy became faster. For men, runners from Belgium, Canada and Japan became slower. Between 1998 and 2011, the ten best race times were achieved by Japanese runners for both women with ~457 min and men with ~393 min [14]. In ultra-marathons longer than the 100 km, athletes from other countries seemed to dominate participation and performance. Ultra-marathoners competing in the world's most famous races 'Badwater' (USA) and 'Spartathlon' (Greece) originated from different regions [15]. In 'Badwater', most of the finishes were achieved by athletes originating from the USA, followed by athletes from Germany and Great Britain. In 'Spartathlon', however, the highest number of finishes was obtained by athletes from Japan, followed by athletes from Germany and France. Regarding performance, however, athletes from other countries were dominating. In 'Badwater', women from the USA were the fastest, followed by women from Canada. For men, the fastest finishes were achieved by competitors from the USA, followed by athletes from Mexico and Canada. In 'Spartathlon', the fastest female finishes were obtained by women from Japan, followed by women from Germany and the USA. In men, the fastest finishes were achieved by runners from Greece, followed by athletes from Japan and Germany [15]. In the 'Marathon des Sables' held in the Moroccan desert, local athletes seemed to dominate [8]. In men, Moroccans won nine of ten competitions, and one edition was won by a Jordanian athlete. In women, however, eight races were won by Europeans (*i.e.*

France five, Luxembourg two, and Spain one, respectively), and two events were won by Moroccan runners [8].

### **Are ultra-marathoners different to marathoners?**

Several studies compared recreational marathoners to recreational ultra-marathoners regarding anthropometric [16,17] and training [16-19] characteristics. Most probably, ultra-runners start with a marathon before completing the first ultra-marathon. In ultra-marathoners, the number of previously completed marathons is significantly higher than the number of completed marathons in marathoners. However, recreational marathoners have a faster personal best marathon time than ultra-marathoners. Successful ultra-marathoners have ~8 years of experience in ultra-running. Ultra-marathoners complete more running kilometers in training than marathoners do, but they run more slowly during training than marathoners [18,19].

Marathoners show difference in anthropometry compared to ultra-marathoners. When marathoners were compared to 100-km ultra-marathoners [16], marathoners had a significantly lower calf circumference and a significantly thicker skinfold at pectoral, axilla, and suprailiacal sites compared to ultra-marathoners. When marathoners were compared to 24-hour ultra-marathoners [17], ultra-marathoners were older, had a lower circumference at both the upper arm and thigh, and a lower skinfold thickness at the pectoral, axillary, and suprailiacal sites compared to the marathoners.

Marathoners show also differences in training compared to ultra-marathoners. Marathoners rather rely on a high running speed during training [16] whereas ultra-marathoners rely on a high running volume during training [16,19]. When marathoners were compared to 100-km ultra-marathoners [16], marathoners completed fewer hours and fewer kilometers during the

week, but they were running faster during training than ultra-marathoners. When marathoners were compared to 24-hour ultra-marathoners, the ultra-marathoners were running for more hours per week and completed more kilometers during training, but were running slower than the marathoners [17]. An interesting recent finding was that ultra-marathoners have a greater pain tolerance than controls [20]. This fact might enable ultra-runners to endure longer under different circumstances than others.

### **Predictor variables for successful ultra-marathon running**

In recent years, several studies tried to find the most important predictor variables for a successful outcome in ultra-marathon running. Among these variables, the most important were age [16,21], anthropometric characteristics such as body fat [16,19], body mass index [22] and limb circumferences [23], training characteristics such as running speed [16,19,21] and training volume [16,19,21] and previous experience [24,25].

Regarding anthropometric characteristics, leg skin-fold thickness - which were highly predictive of short-distance runners [26] - were only predictive in bi-variate analyses, but not in multi-variate analyses, with ultra-marathon running performance [24,27]. In ultra-marathoners, body mass index and body fat seemed to be more important anthropometric characteristics [22,28]. In 161-km ultra-marathoners, lower values of body mass index were associated with faster race times [22]. Body fat is also an important anthropometric predictor variable. In 161-km ultra-marathon running, faster men have lower percent body fat values than slower men, and finishers have lower percent body fat than non-finishers [28].

When different characteristics such as skeletal muscle mass, body fat and training characteristics were investigated in multi-variate analyses, body fat and training characteristics were associated with running times in ultra-marathoners [19]. For 100-km



ultra-marathoners, weekly running kilometers and average speed during training were negatively and the sum of skinfolds were positively related to race time [25]. Apart from anthropometric and training characteristics, age seems also to be an important predictor variable for ultra-marathon performance. In 100-km ultra-marathoners, age, body mass, and percent body fat were positively and weekly running kilometers were negatively related to race times [16].

Previous experience seems, however, to be the most important predictor variable in ultra-marathon performance [22,24,29]. For example, personal best marathon time was a predictor variable in mountain ultra-marathoners [22]. In 24-hour ultra-marathoners, anthropometry and training volume seemed not to have a major effect on race performance [24]. However, a fast personal best marathon time seemed to have the only positive association with race performance [24]. To achieve a maximum of kilometers in a 24-hour ultra-marathon, ultra-runners should have a personal best marathon time of ~3 hours 20 minutes and complete a long training run of ~60 km before the race, whereas anthropometric characteristics such as low body fat or low skinfold thicknesses showed no association with performance [29].

### **Performance in women and men and sex difference in performance**

Generally, women compete slower than men in ultra-marathon running [6,30,31]. Coast et al. [31] compared the world best running performances for race distances from 100 m to 200 km. The running speeds were different between women and men with the average difference being 12.4% faster for men. There was a significant slope to the speed difference across distances where longer distances were associated with greater differences [31]. In 24-hour ultra-marathons held between 1977 and 2012, the sex differences were ~5% for all women and men, ~13% for the annual fastest finishers, ~13% for the top ten and ~12% for the top 100 finishers [30].

However, women were able to reduce the sex gap in recent years [6,30,32]. For example, in 24-hour ultra-marathons, the sex differences decreased for the annual fastest to ~17%, for the annual ten fastest to ~11% and for the annual 100 fastest to ~14% [30]. Across years, female and male ultra-marathoners improved performance [6,32]. In 100-mile ultra-marathons, the fastest women and men improved their race time by ~14% across the 1998-2011 period [32].

### **The age of peak ultra-marathon performance**

The age of peak ultra-marathon performance and a potential change in the age of peak performance has been intensively investigated in very recent years [5,6,30,32,33-36].

Generally, the best ultra-marathon performance is achieved at higher ages than the best marathon performance. The fastest marathoners achieved their best times at the age of ~29.8 years for women and ~28.9 years for men [37]. In 100-km ultra-marathon running, the best race times were observed between 30 and 49 years for men and between 30 and 54 years for women [34]. In 161-km ultra-marathoners, the fastest times were achieved by athletes ranked in the 30-39 year age group for men and the 40-49 year age group for women [38].

Generally, women achieved the best ultra-marathon performance at about the same age like men [30,32]. For 100-km ultra-marathoners, the age of the fastest female and male finishers remained unchanged at ~35 years between 1960 and 2012 [33]. In 24-hour ultra-marathoners, the best performances were achieved at ~40-42 years [35].

In some instances, the age of the fastest finishers increased across years [6], in other instances, it remained unchanged [30,32] or it even decreased [5]. For example, in the annual fastest male 24- hour ultra-marathoners, the age of peak running speed increased from 23 years (1977) to 53 years (2012) [30]. There seemed to be a trend that the fastest finishers were

older in the very long ultra-marathon distances [30,32]. In 100-mile ultra-marathoners, the mean ages of the annual top ten fastest runners were ~39 years for women and ~37 years for men [32]. In 24-hour ultra-marathoners, the ages of peak running speed were unchanged at ~41 and ~44 years for the annual ten and the annual 100 fastest men, respectively. For women, the ages of the annual fastest, the annual ten fastest and the annual 100 fastest remained unchanged at ~43 years, respectively [30]. In 'Badwater' and 'Spartathlon' as two of the toughest ultra-marathons in the world, the fastest race times were achieved by athletes at the age of ~40-42 years [36].

Generally, the number of master ultra-marathoners increased and their performance improved in recent years [39,40]. For example, in the 'Swiss Alpine Marathon, the number of women older than 30 years and men older than 40 years increased and performance improved in women aged 40-44 years [40]. In the 'Marathon des Sables', the number of finishers of masters runners older than 40 years increased for both sexes and men aged 35 to 44 years improved running speed [39]. A potential explanation for the rather high age of ultra-marathoners could be the finding that the median age at the first ultra-marathon was 36 years in the study of Hoffman and Krishnan [3] when investigating 1,345 current and former ultra-marathoners.

### **Energetic demands during ultra-marathon running**

Successful completion of an ultra-marathon such as the 161-km 'Western States Endurance Run' is related to large consumption rates of fuel, fluid, and sodium [41]. During ultra-marathon running, the most important energy source is carbohydrates [42-44]. In 100-km ultra-marathoners, 88.6% derived from carbohydrate, 6.7% from fat, and 4.7% from protein [44]. In one ultra-marathoner completing a 1,005-km race over nine days, the nutrient analysis showed an average daily energy intake of 25,000 kJ with 62% from carbohydrate, 27% from

fat, and 11% from protein. Carbohydrate intake was estimated to be 16.8 g/kg/day and protein intake was estimated to be 2.9 g/kg/day [43].

Generally, ultra-marathoners are not able to meet their energetic demands during a race [45,46] and a partially considerable energy deficit results [45,47,48]. The insufficient energy intake in ultra-endurance athletes is also associated with a low antioxidant vitamin intake [46]. The large energy deficit is caused by inadequate energy intake, possibly due to suppressed appetite and gastrointestinal problems [45]. Ultra-marathoners often suffer from problems with digestion [49] and gastrointestinal bleeding after an ultra-marathon is not uncommon [50]. It has been shown that lower gastrointestinal symptoms correlate with gastrointestinal bleeding [50]. In a mountain ultra-marathon, forty-three percent of all subjects complained of gastro-intestinal distress during the race [49]. A potential reason for these problems could be that exercise has been found to alter esophageal motility [51]. However, also pre-race experience could be an explanation. Runners with gastrointestinal distress tended to complete fewer training miles and to do shorter training runs [52]. The result of the energy deficit is a decrease in body mass where both lean body mass (skeletal muscle mass) and fat mass will be reduced [53,54].

### **Fluid and electrolyte metabolism during ultra-running**

Ultra-marathoners need to consume large amounts of fluids to prevent dehydration during running. During ultra-marathon running, the largest decreases in body mass occur in the first hours of the race [55]. Large fluid intakes might, however, lead to an increased risk for exercise-associated hyponatremia, defined as plasma sodium concentration  $[Na^+] < 135$  mmol/l. Several cases of hyponatremia, with symptoms including altered mentation, seizures, and pulmonary edema, have been reported in endurance athletes over the last few years. This condition has been observed most frequently in individuals participating in ultra-distance

events but has also been reported in marathon runners. Excessive water intake has been identified as a common etiological factor [56].

However, there seemed to be no need to consume excessive amounts of fluid in ultra-marathon running [57]. Generally, ultra-marathoners seemed not to overdrink [58] and no fluid overload should occur during an ultra-marathon [59]. In a 100-km ultra-marathon, faster runners drank more fluid than slower runners and faster runners lost more body mass than slower runners. Additionally, runners lost more body mass when they drank less fluid [57]. Faster running speeds were associated with larger body mass losses. Therefore, athletes who drink less during ultra-marathon running may profit from body mass loss and complete the race faster [57]. Also in a 160-km ultra-marathon, greater loss in body mass during the race was not associated with impaired performance but was rather an aspect of superior performance [60].

### **Exercise-associated hyponatremia in ultra-marathon running**

Exercise-associated hyponatremia is a rather frequently found electrolyte disorder in ultra-marathoners [11,61-63] where high ambient temperatures might be of high importance [11,64]. In a 5-stage 225 km multi-stage ultra-marathon where athletes competed at temperatures of up to 40 °C, the prevalence of exercise-associated hyponatremia amounted to 42% [11]. In the 2008 'Rio Del Lago 100-Mile Endurance Run' in Granite Bay, California, the prevalence of exercise-associated hyponatremia was at 51.2% [64].

Exercise-associated hyponatremia is relatively uncommon in temperate climates [65-69]. In a 7-stage 350-km multi-stage mountain ultra-marathon at moderate to low temperatures, the prevalence of exercise-associated hyponatremia was at 8% [66]. In a 100-km ultra-marathon

[67,68] and a 24-hour run [69] held at moderate to low temperatures, no cases of exercise-associated hyponatremia were recorded.

The country where the ultra-marathon is held seemed to be of importance. In races held in the USA, the prevalence of exercise-associated hyponatremia was higher than in races held in Europe. In the 2009 edition of the 'Western States Endurance Run', the prevalence of EAH was 30% [61]. In ultra-marathons held in Switzerland, Europe, the prevalence of exercise-associated hyponatremia was between 0% and 8% [66,67,69]. Also in ultra-marathoners competing in the Czech Republic, Europe, the prevalence of exercise-associated hyponatremia was low [70].

An increased fluid intake during ultra-marathon running might also have negative effects on the feet since recent studies showed an association between fluid intake and limb swellings [71,72]. Fluid intake was related to the changes in limb volumes, where athletes with an increased fluid intake developed an increase in limb volumes [71]. An increase in feet volume after a 100-km ultra-marathon was due to an increased fluid intake [72].

### **Pathophysiological effects of ultra-marathon running**

Running an ultra-marathon may lead to other disturbances apart from exercise-associated hyponatremia. Ultra-marathon running is associated with a wide range of significant changes in hematological parameters, several of which are injury related. A single bout of strenuous running exercise results in perturbations to numerous biomarkers and the magnitude of changes to biomarkers are proportional to the severity of the running bout [73]. Ultra-marathon running can produce changes to biomarkers that are normally associated with pathology of the muscles, liver and heart [74-76]. However, also markers of the inflammatory response such as C-reactive protein [77-79] and IL-6 [77,79,80] become elevated. Examples

for biomarkers of pathology of muscles, liver and heart are cardiac troponins, plasma volume, myoglobin, leucocytes, sodium, chloride, urea, alkaline phosphatase, gamma-glutamyltransferase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine kinase, bilirubin, total protein, albumin, glucose, calcium, and phosphate [73-76,80-82]. A number of variables remain within normal limits despite severe physical stress [80]. These changes are transient and full recovery generally occurs within days and without any apparent long-term adverse consequences [73,76]. For example, a 48-h ultra-marathon caused hypocapnic alkalosis with slight hyperkalemia and hypocalcemia, but no hyponatremia. Blood biochemistry showed severe muscle but not liver damage, and an acute inflammatory response [83]. Most of the changes were dissolved after 48 hours of recovery [83].

Prolonged running is also known to induce hemolysis. It has been suggested that hemolysis may lead to a significant loss of red blood cells [84]. However, in a 166-km mountain ultra-endurance marathon, 'exercise anemia' was entirely due to plasma volume expansion and not to a concomitant decrease in total red blood cell volume [84].

Apart from these biomarkers, also changes in hormones have been documented [85,86]. After a 110-km ultra-marathon, cortisol was increased and testosterone decreased [85]. In the 1000 km Sydney to Melbourne ultra-marathon, resting serum conjugated catecholamines such as epinephrine, norepinephrine, dopamine, free epinephrine and free dopamine were significantly elevated above the normal mean [86]. Adrenocorticotrophic hormone (ACTH) levels were significantly elevated above the normal range. Immunoreactive beta-endorphin, growth hormone, prolactin, testosterone, cortisol and cortisol-binding globulin were within the normal range. After the race, catecholamines, free and conjugated, remained significantly elevated above the normal mean. ACTH remained elevated and immunoreactive beta-

endorphin within the normal range. A significant increase in growth hormone, prolactin, and cortisol was seen, with no change in cortisol-binding globulin. The authors concluded that these ultra-marathoners demonstrated a significantly altered baseline hormonal state as a model of chronic physical stress [86]. This may represent hormonal adaptation to prolonged stress.

### **Ultra-running and skeletal muscle damage**

Ultra-marathon running has a major impact on skeletal muscles [74]. Unfamiliar exercise involving forceful eccentric muscle contractions, such as running downhill, can cause increases in creatine kinase (CK) and delayed onset of muscle soreness that peaks ~36-72 h after the exercise bout [73]. In ultra-marathoners, a partially considerable increase in CK can be found post-race [63,74,78,87]. For example, CK was increased 35-fold at the end of a 200-km race and remained increased until day 5 [78]. In another 200-km ultra-marathon, CK increased 90-fold post-race [74]. In 'Badwater', CK can increase up to 27,951 U/l [87]. And in the 161-km 'Western States Endurance Run', 216 (66%) of 328 finishers had median and mean CK concentrations of 20,850 U/l and 32,956 U/l, respectively, with a range of 1,500-264,300 U/l, and 13 (6%) of the finishers had values greater than 100,000 U/l [88].

The increase in CK seemed to be dependent upon the fitness level of the athlete [63]. Higher levels of training, or previous ultra-marathon racing experience, or both, were associated with lower immediate post-exercise levels of plasma enzyme activity [63].

Several studies showed that ultra-marathon running leads to a substantial decrease in skeletal muscle mass [57,89,90]. It has been tried to prevent the decrease in skeletal muscle mass by the intake of amino acids [89]. However, BCAA-supplementation before and during a 100-km



ultra-marathon had no effect on performance, skeletal muscle damage [89] (Knechtle et al. 2012b) and muscle soreness [90].

### **Ultra-running and heart damage**

Several studies investigated a potential damage of ultra-running to the heart since cardiac muscle injury markers such as CK, creatine kinase-myocardial band (CK-MB), cardiac troponin I (cTnI) and cardiac muscle strain marker, N-terminal pro-brain natriuretic peptide (NT-proBNP) were elevated post-race [87,91,92]. Also highly-sensitive troponin I was released during ultra-marathon running [93,94].

The findings whether a damage of the heart muscle occurs or not are controversial. High-intensity endurance exercise is associated with biochemical abnormalities that may reflect adverse consequences on cardiac structure and biology [94]. In 18 male marathoners with average age of ~53 years competing in a 308-km ultra-marathon, a normal CK-MB mass index (<5.0 ng/mL) and the absence of an increase in the cTnI levels after the ultra-marathon suggested that no myocardial injury despite an elevation in CK-MB occurred [91]. Also in ultra-marathoners competing in 'Badwater', strenuous endurance exercise under extreme environmental conditions did not result in structural myocardial damage in well-trained ultra-endurance athletes [87]. Matin et al. [95] showed in 77% of ultra-marathoners an elevated activity of serum CK-MB, but cardiac scintigraphy showed no evidence of myocardial injury.

On the other side, in a study investigating competitors in the 2-day 'Lowe Alpine Mountain Marathon', echocardiographic results indicated left ventricular diastolic and systolic dysfunction following cessation of exercise [96]. Humoral markers of cardiac damage were elevated and the elevations of cardiac troponin were suggestive of minimal myocardial damage [96]. After a 24 hour ultra-marathon, two of twenty runners showed a slight increase

in Troponin levels. One of them also had simultaneous decrease in left ventricular ejection fraction. Basal echocardiography assessment showed left ventricular hypertrophy in one and increased left atrial volume in five runners [97]. Estorch et al. [98] showed in runners that myocardial MIBG (123I-metaiodobenzylguanidine) activity was decreased after a 4 hour run. The degree of reduction of myocardial MIBG activity was related to the distance covered. In a 160-km ultra-marathon, reductions in left ventricular function were not significantly associated with changes in cardiac biomarkers [92]. After a 24-hour ultra-marathon, the stroke dimension and ejection phase indexes continued to decline within the last 6 hours of the race but returned to the prerace level 2 to 3 days after the race [99]. Although the stress of an ultra-marathon resulted in a mild reduction in left ventricular function and biomarker release, the mechanisms behind such consequences remain unknown [92].

### **Ultra-running and the immune system**

It is known that strenuous exercise is associated with tissue damage. This activates the innate immune system and local inflammation [100]. In experienced ultra-endurance runners, alterations in immunoglobulin concentrations after a race suggest an enhanced immune response. These alterations may have a role in the maintenance of subject health after an ultra-marathon [100].

Ultra-marathoners often suffer post-race upper-respiratory-tract infections [101,102]. In the ‘Two Oceans Marathon’ in Cape Town, symptoms of upper-respiratory-tract infection occurred in 33.3% of runners compared with 15.3% of controls, and were most common in those who achieved the faster race times [101]. The incidence in slow runners was no greater than that in controls [101]. Vitamin C supplementation may enhance resistance to post-race upper-respiratory-tract infections that occur commonly in competitive ultra-marathon runners and may reduce the severity of such infections [102].

## **Problems of the locomotor system**

Ultra-running can cause minor problems to the skeletal muscle such as muscle soreness but also major problems to tendons and joints [103-105]. Different recent studies using MRI (magnetic resonance imaging) provided detailed analyses of the problems of the locomotor system such as bursal or presumed peritendineal fluid and/or edematous tissue, cartilage defects or tibiotalar bone edema-like lesions [106].

The main running-related musculoskeletal injuries in ultra-marathoners were Achilles tendinopathy and patellofemoral syndrome [105]. However, it is even possible to run across a continent without an injury [107]. Despite the extreme nature and harsh environments of multiday ultra-marathon races, the majority of injuries or illnesses are minor in nature [103,108]. For example, during a 219-km 5-day stage race, lower limb musculoskeletal injuries accounted for 22.2%, predominantly affecting the knee [109]. In the 1005 km Sydney to Melbourne ultra-marathon, 64 injuries were found in 32 runners [103]. The knee (31.3%) and ankle (28.1%) regions were most commonly injured. The most common single diagnosis was retropatellar pain syndrome, and Achilles tendinitis and medial tibial stress syndrome were the next most common injuries. Peritendinitis/tendinitis of the tendons passing under the extensor retinaculum at the ankle was common with 19% of all injuries. In longer ultra-marathons such as 6-day race, Achilles tendonitis, patellofemoral pain, and tendonitis of the foot dorsiflexors were the three most common injuries [110]). In a 6-day race, the overall rate of injuries sufficiently severe to affect running performance was 60% [111]. In the 'Trans Europe FootRace' 2009, a 4,487 km multistage ultra-marathon covering the south of Europe (Bari, Italy) to the North Cape an increase in the diameter of the Achilles tendon, intraosseous signals, bone lesions and subcutaneous oedema were found [104]. Interestingly, an increase of diameter of the Achilles tendon and bone signals were thought to be adaptive; subcutaneous oedema and plantar fascia oedema were related to abortion of the race [104].

## Conclusion

Although we know a lot about physiology, anthropometry, training and performance in these ultra-marathoners, we do not know why these persons compete in these races, what motivates them and why the number of master ultra-marathoners increases across years.

## References

- [1] Ultramarathon running; <http://www.ultramarathonrunning.com/> (Accessed on April 2014)
- [2] Hoffman MD, Fogard K. Demographic characteristics of 161-km ultramarathon runners. *Res Sports Med.* 2012;20(1):59-69.
- [3] Hoffman MD, Krishnan E. Exercise behavior of ultramarathon runners: baseline findings from the ULTRA study. *J Strength Cond Res.* 2013;27(11):2939-45.
- [4] Hoffman MD, Ong JC, Wang G. Historical analysis of participation in 161 km ultramarathons in North America. *Int J Hist Sport.* 2010;27(11):1877-91.
- [5] Fonseca-Engelhardt K, Knechtle B, Rüst CA, Knechtle P, Lepers R, Rosemann T. Participation and performance trends in ultra-endurance running races under extreme conditions - 'Spartathlon' versus 'Badwater'. *Extrem Physiol Med.* 2013;2(1):15.
- [6] Eichenberger E, Knechtle B, Rüst CA, Rosemann T, Lepers R. Age and sex interactions in mountain ultramarathon running - the Swiss Alpine Marathon. *Open Access J Sports Med.* 3:73-80. 2012.
- [7] Krouse RZ, Ransdell LB, Lucas SM, Pritchard ME. Motivation, goal orientation, coaching, and training habits of women ultrarunners. *J Strength Cond Res.* 2011 Oct;25(10):2835-42.
- [8] Knoth C, Knechtle B, Rüst CA, Rosemann T, Lepers R. Participation and performance trends in multistage ultramarathons-the 'Marathon des Sables' 2003-2012. *Extrem Physiol Med.* 2012 ;1(1):13.
- [9] Parise CA, Hoffman MD. Influence of temperature and performance level on pacing a 161 km trail ultramarathon. *Int J Sports Physiol Perform.* 2011;6(2):243-51.
- [10] Wegelin JA, Hoffman MD. Variables associated with odds of finishing and finish time in a 161-km ultramarathon. *Eur J Appl Physiol.* 2011;111(1):145-53.
- [11] Costa RJ, Teixeira A, Rama L, Swancott AJ, Hardy LD, Lee B, Camões-Costa V, Gill S, Waterman JP, Freeth EC, Barrett E, Hankey J, Marczak S, Valero-Burgos E, Scheer V, Murray A, Thake CD. Water and sodium intake habits and status of ultra-endurance runners during a multi-stage ultra-marathon conducted in a hot ambient environment: an observational field based study. *Nutr J.* 2013;12:13.

- [12] Larsen HB. Kenyan dominance in distance running. *Comp Biochem Physiol A Mol Integr Physiol*. 2003;136(1):161-70.
- [13] Wilber RL, Pitsiladis YP. Kenyan and Ethiopian distance runners: what makes them so good? *Int J Sports Physiol Perform*. 2012;7(2):92-102.
- [14] Cejka C, Knechtle B, Knechtle P, Rüst CA, Rosemann T. An increased fluid intake leads to feet swelling in 100-km ultra-marathoners - an observational field study. *J Int Soc Sports Nutr*. 2012;9(1):11.
- [15] Knechtle B, Rüst CA, Rosemann T. The aspect of nationality in participation and performance in ultra-marathon running – a comparison between ‘Badwater’ and ‘Spartathlon’. *OA Sports Medicine*. 2013; 1:1.
- [16] Rüst CA, Knechtle B, Knechtle P, Rosemann T. Similarities and differences in anthropometry and training between recreational male 100-km ultra-marathoners and marathoners. *J Sports Sci*. 2012;30(12):1249-57.
- [17] Rüst CA, Knechtle B, Knechtle P, Rosemann T. Comparison of anthropometric and training characteristics between recreational male marathoners and 24-hour ultramarathoners. *Open Access J Sports Med*. 2012;3:121-9.
- [18] Knechtle B. Ultramarathon runners: nature or nurture? *Int J Sports Physiol Perform*. 2012;7(4):310-2.
- [19] Knechtle B, Rüst CA, Knechtle P, Rosemann T. Does muscle mass affect running times in male long-distance master runners? *Asian J Sports Med*. 2012;3(4):247-56.
- [20] Freund W, Weber F, Billich C, Birklein F, Breimhorst M, Schuetz UH. Ultra-marathon runners are different: investigations into pain tolerance and personality traits of participants of the TransEurope FootRace 2009. *Pain Pract*. 2013;13(7):524-32.
- [21] Knechtle B, Knechtle P, Rosemann T, Lepers R. Predictor variables for a 100-km race time in male ultra-marathoners. *Percept Mot Skills*. 2010;111(3):681-93.
- [22] Hoffman MD. Anthropometric characteristics of ultramarathoners. *Int J Sports Med*. 2008 ;29(10):808-11.
- [23] Knechtle B, Knechtle P, Schulze I, Kohler G. Upper arm circumference is associated with race performance in ultra-endurance runners. *Br J Sports Med*. 2008;42(4):295-9;
- [24] Knechtle B, Wirth A, Knechtle P, Zimmermann K, Kohler G. Personal best marathon performance is associated with performance in a 24-h run and not anthropometry or training volume. *Br J Sports Med*. 2009;43(11):836-9.
- [25] Knechtle B, Knechtle P, Rosemann T, Senn O. What is associated with race performance in male 100-km ultra-marathoners--anthropometry, training or marathon best time? *J Sports Sci*. 2011;29(6):571-7.
- [26] Arrese AL, Ostáriz ES. Skinfold thicknesses associated with distance running performance in highly trained runners. *J Sports Sci*. 2006;24(1):69-76.

- [27] Knechtle B, Knechtle P, Rüst CA, Rosemann T. Leg skinfold thicknesses and race performance in male 24-hour ultra-marathoners. *Proc (Bayl Univ Med Cent)*. 2011;24(2):110-4.
- [28] Hoffman MD, Lebus DK, Ganong AC, Casazza GA, Van Loan M. Body composition of 161-km ultramarathoners. *Int J Sports Med*. 2010;31(2):106-9.
- [29] Knechtle B, Knechtle P, Rosemann T, Lepers R. Personal best marathon time and longest training run, not anthropometry, predict performance in recreational 24-hour ultrarunners. *J Strength Cond Res*. 2011;25(8):2212-8.
- [30] Peter L, Rüst CA, Knechtle B, Rosemann T, Lepers R. Sex differences in 24-hour ultra-marathon performance - A retrospective data analysis from 1977 to 2012. *Clinics (Sao Paulo)*. 2014;69(1):38-46.
- [31] Coast JR, Blevins JS, Wilson BA. Do gender differences in running performance disappear with distance? *Can J Appl Physiol*. 2004;29(2):139-45.
- [32] Rüst CA, Knechtle B, Rosemann T, Lepers R. Analysis of performance and age of the fastest 100-mile ultra-marathoners worldwide. *Clinics (Sao Paulo)*. 2013;68(5):605-11.
- [33] Cejka N, Knechtle B, Rüst CA, Rosemann T, Lepers R. Performance and age of the fastest female and male 100-km ultra-marathoners worldwide from 1960 to 2012. *J Strength Cond Res*; 2014. [Epub ahead of print]
- [34] Knechtle B, Rüst CA, Rosemann T, Lepers R. Age-related changes in 100-km ultra-marathon running performance. *Age (Dordr)*. 2012;34(4):1033-45.
- [35] Zingg M, Rüst CA, Lepers R, Rosemann T, Knechtle B. Master runners dominate 24-h ultramarathons worldwide-a retrospective data analysis from 1998 to 2011. *Extrem Physiol Med*. 2013;2(1):21.
- [36] Zingg MA, Knechtle B, Rüst CA, Rosemann T, Lepers R. Analysis of participation and performance in athletes by age group in ultramarathons of more than 200 km in length. *Int J Gen Med*. 2013;6:209-20.
- [37] Hunter SK, Stevens AA, Magennis K, Skelton KW, Fauth M. Is there a sex difference in the age of elite marathon runners? *Med Sci Sports Exerc*. 2011;43(4):656-64.
- [38] Hoffman MD. Performance trends in 161-km ultramarathons. *Int J Sports Med*. 2010;31(1):31-7.
- [39] Jampen SC, Knechtle B, Rüst CA, Lepers R, Rosemann T. Increase in finishers and improvement of performance of masters runners in the Marathon des Sables. *Int J Gen Med*. 2013;6:427-38.
- [40] Rüst CA, Knechtle B, Eichenberger E, Rosemann T, Lepers R. Finisher and performance trends in female and male mountain ultramarathoners by age group. *Int J Gen Med*. 2013;6:707-18.

- [41] Stuempfle KJ, Hoffman MD, Weschler LB, Rogers IR, Hew-Butler T. Race diet of finishers and non-finishers in a 100 mile (161 km) mountain footrace. *J Am Coll Nutr*. 2011;30(6):529-35.
- [42] Case S, Evans D, Tibbets G, Case S, Miller D. Dietary intakes of participants in the IditaSport Human Powered Ultra-marathon. *Alaska Med*. 1995;37(1):20-4.
- [43] Eden BD, Abernethy PJ. Nutritional intake during an ultraendurance running race. *Int J Sport Nutr*. 1994;4(2):166-74.
- [44] Fallon KE, Broad E, Thompson MW, Reull PA. Nutritional and fluid intake in a 100-km ultramarathon. *Int J Sport Nutr*. 1998;8(1):24-35.
- [45] Enqvist JK, Mattsson CM, Johansson PH, Brink-Elfegoun T, Bakkman L, Ekblom BT. Energy turnover during 24 hours and 6 days of adventure racing. *J Sports Sci*. 2010;28(9):947-55.
- [46] Machefer G, Groussard C, Zouhal H, Vincent S, Youssef H, Faure H, Malardé L, Gratas-Delamarche A. Nutritional and plasmatic antioxidant vitamins status of ultra endurance athletes. *J Am Coll Nutr*. 2007;26(4):311-6.
- [47] Hill RJ, Davies PS. Energy expenditure during 2 wk of an ultra-endurance run around Australia. *Med Sci Sports Exerc*. 2001;33(1):148-51.
- [48] O'Hara WJ, Allen C, Shephard RJ, Gill JW. LaTulippe--a case study of a one hundred and sixty kilometre runner. *Br J Sports Med*. 1977;11(2):83-7.
- [49] Rehrer NJ, Brouns F, Beckers EJ, Frey WO, Villiger B, Riddoch CJ, Menheere PP, Saris WH. Physiological changes and gastro-intestinal symptoms as a result of ultra-endurance running. *Eur J Appl Physiol Occup Physiol*. 1992;64(1):1-8.
- [50] Baska RS, Moses FM, Graeber G, Kearney G. Gastrointestinal bleeding during an ultramarathon. *Dig Dis Sci*. 1990;35(2):276-9.
- [51] Simons SM, Kennedy RG. Gastrointestinal problems in runners. *Curr Sports Med Rep*. 2004;3(2):112-6.
- [52] Glace B, Murphy C, McHugh M. Food and fluid intake and disturbances in gastrointestinal and mental function during an ultramarathon. *Int J Sport Nutr Exerc Metab*. 2002;12(4):414-27.
- [53] Knechtle B, Wirth A, Knechtle P, Rosemann T, Senn O. Do ultra-runners in a 24-h run really dehydrate? *Ir J Med Sci*. 2011;180(1):129-34. 30.
- [54] Schütz UH, Billich C, König K, Würslin C, Wiedelbach H, Brambs HJ, Machann J. Characteristics, changes and influence of body composition during a 4486 km transcontinental ultramarathon: results from the TransEurope FootRace mobile whole body MRI-project. *BMC Med*. 2013;11:122.

- [55] Kao WF, Shyu CL, Yang XW, Hsu TF, Chen JJ, Kao WC, Polun-Chang, Huang YJ, Kuo FC, Huang CI, Lee CH. Athletic performance and serial weight changes during 12- and 24-hour ultra-marathons. *Clin J Sport Med*. 2008;18(2):155-8.
- [56] Barr SI, Costill DL. Water: can the endurance athlete get too much of a good thing? *J Am Diet Assoc*. 1989;89(11):1629-32.
- [57] Knechtle B, Knechtle P, Wirth A, Alexander Rüst C, Rosemann T. A faster running speed is associated with a greater body weight loss in 100-km ultra-marathoners. *J Sports Sci*. 2012;30(11):1131-40.
- [58] Knechtle B, Knechtle P, Rosemann T. Do male 100-km ultra-marathoners overdrink? *Int J Sports Physiol Perform*. 2011;6(2):195-207.
- [59] Knechtle B, Senn O, Imoberdorf R, Joleska I, Wirth A, Knechtle P, Rosemann T. No fluid overload in male ultra-runners during a 100 km ultra-run. *Res Sports Med*. 2011;19(1):14-27.
- [60] Landman ZC, Landman GO, Fatehi P. Physiologic alterations and predictors of performance in a 160-km ultramarathon. *Clin J Sport Med*. 2012;22(2):146-51.
- [61] Hoffman MD, Stuenkel KJ, Rogers IR, Weschler LB, Hew-Butler T. Hyponatremia in the 2009 161-km Western States Endurance Run. *Int J Sports Physiol Perform*. 2012; 7(1):6-10.
- [62] Knechtle B, Knechtle P, Rosemann T. Low prevalence of exercise-associated hyponatremia in male 100 km ultra-marathon runners in Switzerland. *Eur J Appl Physiol*. 2011;111(6):1007-16.
- [63] Noakes TD, Carter JW. The responses of plasma biochemical parameters to a 56-km race in novice and experienced ultra-marathon runners. *Eur J Appl Physiol Occup Physiol*. 1982;49(2):179-86.
- [64] Lebus DK, Casazza GA, Hoffman MD, Van Loan MD. Can changes in body mass and total body water accurately predict hyponatremia after a 161-km running race? *Clin J Sport Med*. 2010;20(3):193-9.
- [65] Cuthill JA, Ellis C, Inglis A. Hazards of ultra-marathon running in the Scottish Highlands: exercise-associated hyponatraemia. *Emerg Med J*. 2009 ;26(12):906-7.
- [66] Knechtle B, Knechtle P, Rüst CA, Gnädinger M, Imoberdorf R, Kohler G, Rosemann T, Ballmer P. Regulation of electrolyte and fluid metabolism in multi-stage ultra-marathoners. *Horm Metab Res*. 2012;44(12):919-26. 25.
- [67] Bürge J, Knechtle B, Knechtle P, Gnädinger M, Rüst CA, Rosemann T. Maintained serum sodium in male ultra-marathoners--the role of fluid intake, vasopressin, and aldosterone in fluid and electrolyte regulation. *Horm Metab Res*. 2011;43(9):646-52.
- [68] Knechtle B, Senn O, Imoberdorf R, Joleska I, Wirth A, Knechtle P, Rosemann T. Maintained total body water content and serum sodium concentrations despite body mass loss



in female ultra-runners drinking ad libitum during a 100 km race. *Asia Pac J Clin Nutr*. 2010;19(1):83-90.

[69] Knechtle B, Knechtle P, Rosemann T. No exercise-associated hyponatremia found in an observational field study of male ultra-marathoners participating in a 24-hour ultra-run. *Phys Sportsmed*. 2010;38(4):94-100.

[70] Chlíbková D, Knechtle B, Rosemann T, Zákovská A, Tomášková I. The prevalence of exercise-associated hyponatremia in 24-hour ultra-mountain bikers, 24-hour ultra-runners and multi-stage ultra-mountain bikers in the Czech Republic. *J Int Soc Sports Nutr*. 2014;11(1):3.

[71] Bracher A, Knechtle B, Gnädinger M, Bürge J, Rüst CA, Knechtle P, Rosemann T. Fluid intake and changes in limb volumes in male ultra-marathoners: does fluid overload lead to peripheral oedema? *Eur J Appl Physiol*. 2012 ;112(3):991-1003.

[72] Cejka N, Rüst CA, Lepers R, Onywera V, Rosemann T, Knechtle B. Participation and performance trends in 100-km ultra-marathons worldwide. *J Sports Sci*; 2013. [Epub ahead of print]

[73] Bird SR, Linden M, Hawley JA. Acute changes to biomarkers as a consequence of prolonged strenuous running. *Ann Clin Biochem*; 2013 [Epub ahead of print]

[74] Kim HJ, Lee YH, Kim CK. Biomarkers of muscle and cartilage damage and inflammation during a 200 km run. *Eur J Appl Physiol*. 2007;99(4):443-7.

[75] Nagel D, Seiler D, Franz H, Jung K. Ultra-long-distance running and the liver. *Int J Sports Med*. 1990;11(6):441-5.

[76] Wu HJ, Chen KT, Shee BW, Chang HC, Huang YJ, Yang RS. Effects of 24 h ultra-marathon on biochemical and hematological parameters. *World J Gastroenterol*. 2004;10(18):2711-4.

[77] Kasprowicz K, Ziemann E, Ratkowski W, Laskowski R, Kaczor JJ, Dadci R, Antosiewicz J. Running a 100-km ultra-marathon induces an inflammatory response but does not raise the level of the plasma iron-regulatory protein hepcidin. *J Sports Med Phys Fitness*. 2013;53(5):533-7.

[78] Kim HJ, Lee YH, Kim CK. Changes in serum cartilage oligomeric matrix protein (COMP), plasma CPK and plasma hs-CRP in relation to running distance in a marathon (42.195 km) and an ultra-marathon (200 km) race. *Eur J Appl Physiol*. 2009;105(5):765-70.

[79] Waśkiewicz Z, Kłapcińska B, Sadowska-Krępa E, Czuba M, Kempa K, Kimsa E, Gerasimuk D. Acute metabolic responses to a 24-h ultra-marathon race in male amateur runners. *Eur J Appl Physiol*. 2012;112(5):1679-88.

[80] Fallon KE, Sivyer G, Sivyer K, Dare A. The biochemistry of runners in a 1600 km ultramarathon. *Br J Sports Med*. 1999;33(4):264-9.

[81] McKechnie JK, Leary WP, Noakes TD. Metabolic responses to a 90 km running race. *S Afr Med J*. 1982;61(13):482-4.

- [82] Saugy J, Place N, Millet GY, Degache F, Schena F, Millet GP. Alterations of neuromuscular function after the world's most challenging mountain ultra-marathon. *PLoS One*. 2013 26;8(6):e65596.
- [83] Kłapcińska B, Waśkiewicz Z, Chrapusta SJ, Sadowska-Krępa E, Czuba M, Langfort J. Metabolic responses to a 48-h ultra-marathon run in middle-aged male amateur runners. *Eur J Appl Physiol*. 2013;113(11):2781-93.
- [84] Robach P, Boisson RC, Vincent L, Lundby C, Moutereau S, Gergelé L, Michel N, Duthil E, Féasson L, Millet GY. Hemolysis induced by an extreme mountain ultra-marathon is not associated with a decrease in total red blood cell volume. *Scand J Med Sci Sports*. 2014;24(1):18-27.
- [85] Fournier PE, Stalder J, Mermillod B, Chantraine A. Effects of a 110 kilometers ultra-marathon race on plasma hormone levels. *Int J Sports Med*. 1997;18(4):252-6.
- [86] Pestell RG, Hurley DM, Vandongen R. Biochemical and hormonal changes during a 1000 km ultramarathon. *Clin Exp Pharmacol Physiol*. 1989;16(5):353-61.
- [87] Roth HJ, Leithäuser RM, Doppelmayr H, Doppelmayr M, Finkernagel H, von Duvillard SP, Korff S, Katus HA, Giannitsis E, Beneke R. Cardiospecificity of the 3rd generation cardiac troponin T assay during and after a 216 km ultra-endurance marathon run in Death Valley. *Clin Res Cardiol*. 2007;96(6):359-64.
- [88] Hoffman MD, Ingwersen JL, Rogers IR, Hew-Butler T, Stuempfle KJ. Increasing creatine kinase concentrations at the 161-km Western States Endurance Run. *Wilderness Environ Med*. 2012 Mar;23(1):56-60.
- [89] Knechtle B, Mrazek C, Wirth A, Knechtle P, Rüst CA, Senn O, Rosemann T, Imoberdorf R, Ballmer P. Branched-chain amino acid supplementation during a 100-km ultra-marathon--a randomized controlled trial. *J Nutr Sci Vitaminol (Tokyo)*. 2012;58(1):36-44.
- [90] Knechtle B, Knechtle P, Mrazek C, Senn O, Rosemann T, Imoberdorf R, Ballmer P. No effect of short-term amino acid supplementation on variables related to skeletal muscle damage in 100 km ultra-runners - a randomized controlled trial. *J Int Soc Sports Nutr*. 2011;8:6.
- [91] Kim YJ, Shin YO, Lee JB, Lee YH, Shin KA, Kim AC, Goh CW, Kim C, Oh JK, Min YK, Yang HM. The effects of running a 308 km ultra-marathon on cardiac markers. *Eur J Sport Sci*. 2014;14 (1): 92-7.
- [92] Scott JM, Esch BT, Shave R, Warburton DE, Gaze D, George K. Cardiovascular consequences of completing a 160-km ultramarathon. *Med Sci Sports Exerc*. 2009;41(1):26-34.
- [93] Lippi G, Schena F, Salvagno GL, Tarperi C, Aloe R, Guidi GC. Comparison of conventional and highly-sensitive troponin I measurement in ultra-marathon runners. *J Thromb Thrombolysis*. 2012;33(4):338-42.
- [94] Salvagno GL, Schena F, Gelati M, Danese E, Cervellin G, Guidi GC, Lippi G. The concentration of high-sensitivity troponin I, galectin-3 and NT-proBNP substantially increase after a 60-km ultramarathon. *Clin Chem Lab Med*. 2014;52(2):267-72.

- [95] Matin P, Lang G, Carretta R, Simon G. Scintigraphic evaluation of muscle damage following extreme exercise: concise communication. *J Nucl Med*. 1983;24(4):308-11.
- [96] Shave RE, Dawson E, Whyte G, George K, Ball D, Gaze DC, Collinson PO. Evidence of exercise-induced cardiac dysfunction and elevated cTnT in separate cohorts competing in an ultra-endurance mountain marathon race. *Int J Sports Med*. 2002;23(7):489-94.
- [97] Passaglia DG, Emed LG, Barberato SH, Guerios ST, Moser AI, Silva MM, Ishie E, Guarita-Souza LC, Costantini CR, Faria-Neto JR. Acute effects of prolonged physical exercise: evaluation after a twenty-four-hour ultramarathon. *Arq Bras Cardiol*. 2013;100(1):21-8.
- [98] Estorch M, Serra-Grima R, Carrió I, Flotats A, Lizárraga A, Bernà LL, Prats T, Segura R. Influence of prolonged exercise on myocardial distribution of 123I-MIBG in long-distance runners. *J Nucl Cardiol*. 1997;4(5):396-402.
- [99] Niemelä KO, Palatsi IJ, Ikäheimo MJ, Takkunen JT, Vuori JJ. Evidence of impaired left ventricular performance after an uninterrupted competitive 24 hour run. *Circulation*. 1984;70(3):350-6.
- [100] McKune AJ, Smith LL, Semple SJ, Wade AA. Influence of ultra-endurance exercise on immunoglobulin isotypes and subclasses. *Br J Sports Med*. 2005;39(9):665-70.
- [101] Peters EM, Bateman ED. Ultramarathon running and upper respiratory tract infections. An epidemiological survey. *S Afr Med J*. 1983;64(15):582-4.
- [102] Peters EM, Goetzsche JM, Grobbelaar B, Noakes TD. Vitamin C supplementation reduces the incidence of postrace symptoms of upper-respiratory-tract infection in ultramarathon runners. *Am J Clin Nutr*. 1993;57(2):170-4.
- [103] Fallon KE. Musculoskeletal injuries in the ultramarathon: the 1990 Westfield Sydney to Melbourne run. *Br J Sports Med*. 1996;30(4):319-23.
- [104] Freund W, Weber F, Billich C, Schuetz UH. The foot in multistage ultra-marathon runners: experience in a cohort study of 22 participants of the Trans Europe Footrace Project with mobile MRI. *BMJ Open*. 2012;2(3).
- [105] Lopes AD, Hespanhol Júnior LC, Yeung SS, Costa LO. What are the main running-related musculoskeletal injuries? A Systematic Review. *Sports Med*. 2012;42(10):891-905.
- [106] Theysohn JM, Kraff O, Maderwald S, Kokulinsky PC, Ladd ME, Barkhausen J, Ladd SC. MRI of the ankle joint in healthy non-athletes and in marathon runners: image quality issues at 7.0 T compared to 1.5 T. *Skeletal Radiol*. 2013;42(2):261-7.
- [107] Lathan SR, Cantwell JD. A run for the record. Studies on a trans-American ultramarathoner. *JAMA*. 1981;245(4):367-8.
- [108] Krabak BJ, Waite B, Schiff MA. Study of injury and illness rates in multiday ultramarathon runners. *Med Sci Sports Exerc*. 2011;43(12):2314-20.

- [109] Scheer BV, Murray A. Al Andalus Ultra Trail: an observation of medical interventions during a 219-km, 5-day ultramarathon stage race. *Clin J Sport Med*. 2011;21(5):444-6.
- [110] Bishop GW, Fallon KE. Musculoskeletal injuries in a six-day track race: ultramarathoner's ankle. *Clin J Sport Med*. 1999;9(4):216-20.
- [111] Hutson MA. Medical implications of ultra marathon running: observations on a six day track race. *Br J Sports Med*. 1984;18(1):44-5.